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(54) Title: TRANSDERMAL PATCH COMPRISING METHYLPHENIDATE

(57) Abstract: Transdermal patches comprising the free base form of methylphenidate are capable of delivering 40 % or more of the entire load of methylphenidate over a 12 hour period.

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TRANSDERMAL PATCH COMPRISING METHYLPHENIDATE

The present application relates to transdermal patches comprising methylphenidate, and to methods of treatment of such conditions as ADHD and narcolepsy, using such patches.

Methylphenidate has long been established as the drug of choice in the treatment of attention deficit disorders, including Attention Deficit Hyperactivity Disorder (ADHD). More recently, methylphenidate has been shown to be effective in the treatment of narcolepsy.

It is estimated that 1 in 1000 people are affected by the neurological sleep disorder, narcolepsy. The most prevalent symptom, excessive daytime sleepiness, frequently manifests in the teens or early twenties, but can also occur later in life. Psychostimulants, such as methylphenidate, show good efficacy in treating the excessive daytime sleepiness symptoms, but the rapid clearance and variable bioavailability of conventional administration forms of the drug make it necessary for multiple doses throughout the day.

The most common form of current therapy of Attention Deficit Disorder (ADD) and ADHD is oral therapy, which requires the optimisation of the dosing of each patient, both to maximise efficacy and to minimise side-effects. Multiple daily dosing of methylphenidate creates significant problems for schools, for example, in storing and administering what is a controlled drug. Sustained release tablets have been introduced, but these fail to overcome the dosing difficulties, since individual doses must still be titrated, while the duration of action often falls short of a single daily dose therapy. In addition, the tablets must *not* be chewed by the patient, a significant problem with children in general, and particularly with ADHD children.

The need for dose titration is due, at least partly, to highly variable intestinal absorption. Oral dosing is also undesirable, as methylphenidate is largely metabolised, on first pass, to ritalinic acid.

It has been proposed to administer a purified stereoisomer of methylphenidate, but this is unlikely to overcome many problems, as the '*d*' enantiomer is not only generally associated with the desirable effects, but also with most of the side-effects. Little is known of the '*l*' enantiomer, owing to stereoselective absorption of the *d* enantiomer in the gut, so that only negligible amounts of the *l* enantiomer are observed in the plasma after oral administration.

EP-A-881216 discloses solid methylphenidate, its preparation and use in medicine and transdermal delivery of the free base.

WO99/30694, to Noven Pharmaceuticals Inc., discloses transdermal patches comprising methylphenidate.

US-A-5834010 discloses transdermal patches comprising, amongst other drugs, methylphenidate, but wherein triacetin is used as a penetration enhancer.

Methylphenidate or, to give it its systematic name, α -phenyl-2-piperidineacetic acid methyl ester, is disclosed in US-A-2957880 to Ciba. In particular, the compound is obtainable from 50 percent alcohol but is practically insoluble in water. Accordingly, the majority of references to methylphenidate, in the art, are, by default, to the hydrochloride salt of methylphenidate, which is highly soluble in water, and which is easily able to be formulated for oral administration. Methylphenidate is commercially available in the form of the hydrochloride salt.

What has now, surprisingly, been found, is that the free base of methylphenidate can be delivered from a transdermal patch at high rates.

Thus, in a first aspect, the present invention provides a transdermal patch comprising the free base form of methylphenidate, wherein the patch is capable of delivering 40% or more of the total methylphenidate comprised therein within 12 hours, *in situ*.

In particular, the adhesives of WO 99/02141 have been found to be useful in the present invention.

Accordingly, in an alternative aspect, there is provided a transdermal patch comprising the free base form of methylphenidate, wherein the methylphenidate is retained by the adhesive, the adhesive comprising a cross-linked block copolymer having drug retention properties, the block copolymer having hard and soft segments, and wherein there is cross-linking between the soft segments.

In addition, it has now been found that methylphenidate patches may be used in the treatment of obesity. Methylphenidate has excellent appetite suppressant activity, and patches provide a continuous supply of methylphenidate to suppress the appetite.

It is an advantage that transdermal patches comprising the free base form of methylphenidate are capable of delivering 40% or more of the entire load of methylphenidate at rates up to 10 times, or more, of other transdermal patches comprising methylphenidate, especially those of WO99/30694, for example.

Delivery by means of a patch has the advantage of avoiding potential drug abuse, as well as overcoming intestinal absorption problems. Further, as an appetite suppressant, there will not be occasions when a single dose tablet is wearing off and the patient becomes hungry. Similarly, with narcoleptics, the non-pulsatile nature of drug delivery avoids spells of low supply which could lead to overwhelming drowsiness.

The patches of the invention also have the significant advantage of being able to be provided in considerably smaller sizes and with substantially lower concentrations of active ingredient than in the art. Thus, we have found that less than 20 mg of the free base in a 20 cm² patch provides a satisfactory therapeutic regimen, in accordance with the present invention. Phase I data suggests that, for most patients, a plasma level of 2 to 5 ng/ml is sustainable with a patch of not more than 20 cm² having a loading of between 0.6 and 1.2 mg/cm². Patches of up to 40 cm² or greater may be necessary for larger patients, and it will be appreciated that such patches may be sub-divided, if necessary. Smaller patients may require smaller patches. Other doses, particularly in accordance with age and weight of patient, as well as the condition to be treated, will be apparent to those skilled in the art.

By "transdermal patch", is meant a system capable of delivery of a drug to a patient *via* the skin, or any suitable external surface, including mucosal membranes, such as those found inside the mouth. Such delivery systems generally comprise a flexible backing, an adhesive and a drug retaining matrix, the backing protecting the adhesive and matrix and the adhesive holding the whole on the skin of the patient. On contact with the skin, the drug-retaining matrix delivers drug to the skin, the drug then passing through the skin into the patient's system.

It will be appreciated that the term "drug" relates to any therapeutically or pharmacologically active substance that it is desired to administer to a patient. While the patches of the present invention specifically require methylphenidate to be provided as the active ingredient, other drugs may also be incorporated in the patches as active ingredients, if desired.

The "free base form" of methylphenidate relates to the form in which the methylphenidate is incorporated into the patch. It will be appreciated that the methylphenidate may be complexed, for example, with elements of the drug-retaining matrix of the patch and, as such, the methylphenidate may not necessarily be in the form of the free base, when actually retained by the patch.

What we have found is that the free base form of methylphenidate is particularly stable in patches of the invention, in contrast to the disclosure of WO99/30694, where stability problems are noted. In particular, no degradation of methylphenidate was detectable in patches containing 10% methylphenidate and 5% IPM stored for six months at 25°C.

While the present invention is not limited to any particular form of transdermal patch, we prefer to employ the type of patch disclosed in our co-pending WO 99/02141, incorporated herein by reference. Also of use are the patches disclosed in co-pending PCT/GB00/00273, incorporated herein by reference. The advantage of such patches is that the adhesive also acts as an excellent drug-retaining matrix and, in WO 99/02141, is comprised of soft and hard segments making up block copolymers, but with the soft segments, rather than the hard segments, being cross-linked. Cross-linking of the soft segments enables the provision of a far greater volume of soft segment portion of the overall adhesive, thereby enabling far greater drug retention, as it is the soft segment that takes up the drug.

Thus, the present invention further provides patches as described above, wherein the adhesive comprises a cross-linked block copolymer, the block copolymer having hard and soft segments wherein there is chemical cross-linking between the soft segments. Preferably, the adhesive comprises plasticiser, as described hereinunder.

In PCT/GB00/00273, similar adhesives are preferably employed, but also comprise plasticiser in substantial amounts. Cohesion of the adhesive is achieved by cross-linking available ketone groups with a polyamine, and the resulting adhesive has excellent drug-loading properties whilst not removing the stratum corneum on removal of the patch. Such adhesives are useful in the present invention.

The patch preferably comprises a drug-impermeable backing layer. Suitable examples of drug-impermeable backing layers which may be used for transdermal or

medicated patches include films or sheets of polyolefins, polyesters, polyurethanes, polyvinyl alcohols, polyvinyl chlorides, polyvinylidene chloride, polyamides, ethylene-vinyl acetate copolymer (EVA), ethylene-ethylacrylate copolymer (EEA), vinyl acetate-vinyl chloride copolymer, cellulose acetate, ethyl cellulose, metal vapour deposited films or sheets thereof, rubber sheets or films, expanded synthetic resin sheets or films, non-woven fabrics, fabrics, knitted fabrics, paper and foils. Preferred drug-impermeable, elastic backing materials are selected from polyethylene terephthalate (PET), polyurethane, ethylene-vinyl acetate copolymer (EVA), plasticised polyvinyl chloride, woven and non-woven fabric. Especially preferred is non-woven polyethylene terephthalate (PET). Other backings will be readily apparent to those skilled in the art.

The term 'block copolymer', in the preferred adhesives of the invention, refers to a macromolecule comprised of two or more chemically dissimilar polymer structures, terminally connected together (Block Copolymers: Overview and Critical Survey, Noshay and McGrath, 1977). These dissimilar polymer structures, sections or segments, represent the 'blocks' of the block copolymer. The blocks may generally be arranged in an A-B structure, an A-B-A structure, or a multi-block $-(A-B)_n-$ system, wherein A and B are the chemically distinct polymer segments of the block copolymer.

It is generally preferred that the block copolymer is of an A-B-A structure, especially wherein one of A and B is an acrylic-type polymeric unit. It will be appreciated that the present invention is also applicable using block copolymers which possess three or more different blocks, such as an A-B-C block copolymer. However, for convenience, reference hereinafter to block copolymers will assume that there are only A and B sub-units, but it will be appreciated that such reference also encompasses block copolymers having more than two different sub-units, unless otherwise specified.

It will be appreciated that the properties of block copolymers are very largely determined by the nature of the A and B blocks. Block copolymers commonly possess both 'hard' and 'soft' segments. A 'hard' segment is a polymer that has a glass transition temperature (T_g) and/or a melting temperature (T_m) that is above room

temperature, while a 'soft' segment is a polymer that has a T_g (and possibly a T_m) below room temperature. The different segments are thought to impart different properties to the block copolymer. Without being constrained by theory, it is thought that association of the hard segments of separate block copolymer units result in physical cross-links within the block copolymer, thereby promoting cohesive properties of the block copolymer. It is particularly preferred that the hard segments of the block copolymers form such physical close associations.

The block copolymers useful in the present invention preferably are acrylic block copolymers. In acrylic block copolymers, at least one of the blocks of the block copolymer is an acrylic acid polymer, or a polymer of an acrylic acid derivative. The polymer may be composed of just one repeated monomer species. However, it will be appreciated that a mixture of monomeric species may be used to form each of the blocks, so that a block may, in itself, be a copolymer. The use of a combination of different monomers can affect various properties of the resulting block copolymer. In particular, variation in the ratio or nature of the monomers used allows properties such as adhesion, tack and cohesion to be modulated, so that it is generally advantageous for the soft segments of the block copolymer to be composed of more than one monomer species.

It is preferred that alkyl acrylates and alkyl methacrylates are polymerised to form the soft portion of the block copolymer. Alkyl acrylates and alkyl methacrylates are thought to provide properties of tack and adhesion. Suitable alkyl acrylates and alkyl methacrylates include n-butyl acrylate, n-butyl methacrylate, hexyl acrylate, 2-ethylbutyl acrylate, isooctyl acrylate, 2-ethylhexyl acrylate, 2-ethylhexyl methacrylate, decyl acrylate, decyl methacrylate, dodecyl acrylate, dodecyl methacrylate, tridecyl acrylate and tridecyl methacrylate, although other suitable acrylates and methacrylates will be readily apparent to those skilled in the art. It is preferred that the acrylic block copolymer comprises at least 50% by weight of alkyl acrylate or alkyl methacrylate (co)polymer.

Variation in the components of the soft segment affects the overall properties of the block copolymer, although the essential feature remains the cross-linking of the soft segments. For example, soft segments essentially consisting of diacetone acrylamide with either butyl acrylate and/or 2-ethylhexyl acrylate, in approximately equal proportions, work well, and a ratio by weight of about 3 : 4 : 4 provides good results. It is preferred that diacetone acrylamide, or other polar monomer, such as hydroxyethyl methacrylate or vinyl acetate, be present in no more than 50% w/w of the monomeric mix of the soft segment, as this can lead to reduced adhesion, for example. The acrylate component may generally be varied more freely, with good results observed with both 2-ethylhexyl acrylate and butyl acrylate together or individually.

As noted above, ratios of the various monomers are generally preferred to be approximately equal. For adhesives, this is preferred to be with a polar component of 50% or less of the soft segment, with the apolar portion forming up to about 85% w/w, but preferably between about 50 and 70% w/w. In the example above, this is about 72% (4+4) apolar to about 18% (3) polar.

In general, it is particularly preferred that any apolar monomer used does not confer acidity on the adhesive. Adhesives of the invention are preferably essentially neutral, and this avoids any unnecessary degeneration of the methylphenidate.

Limiting active functionalities, especially those with active hydrogen, is generally preferred, in order to permit wide use of any given formulation of adhesive without having to take into account how it is likely to interact, chemically, with its environment. Thus, a generally chemically inert adhesive is preferred, in the absence of requirements to the contrary.

As discussed above, polymers suitable for use as the hard portion of the block copolymer possess glass transition temperatures above room temperature. Suitable monomers for use in forming the hard segment polymer include styrene, α -methylstyrene, methyl methacrylate and vinyl pyrrolidone, although other suitable

monomers will be readily apparent to those skilled in the art. Styrene and polymethyl methacrylate have been found to be suitable for use in the formation of the hard segment of the block copolymers. It is preferred that the hard portion of the block copolymer forms from 3 - 30% w/w of the total block copolymer, particularly preferably from 5 - 15% w/w.

The block copolymer is further characterised in that the soft portions contain a degree of chemical cross-linking. Such cross-linking may be effected by any suitable cross-linking agent. It is particularly preferable that the cross-linking agent be in the form of a monomer suitable for incorporation into the soft segment during polymerisation. Preferably the cross-linking agent has two, or more, radically polymerisable groups, such as a vinyl group, per molecule of the monomer, at least one tending to remain unchanged during the initial polymerisation, thereby to permit cross-linking of the resulting block copolymer.

Suitable cross-linking agents for use in the present invention include divinylbenzene, methylene bis-acrylamide, ethylene glycol di(meth)acrylate, ethylene glycol tetra(meth)acrylate, propylene glycol di(meth)acrylate, butylene glycol di(meth)acrylate, or trimethylolpropane tri(meth)acrylate, although other suitable cross-linking agents will be readily apparent to those skilled in the art. A preferred cross-linking agent is tetraethylene glycol dimethacrylate. It is preferred that the cross-linking agent comprises about 0.01 - 0.6% by weight of the block copolymer, with 0.1 - 0.4% by weight being particularly preferred.

Methods for the production of block copolymers from their monomeric constituents are well known. The block copolymer portions of the present invention may be produced by any suitable method, such as step growth, anionic, cationic and free radical methods (Block Copolymers, *supra*). Free radical methods are generally preferred over other methods, such as anionic polymerisation, as the solvent and the monomer do not have to be purified.

Suitable initiators for polymerisation include polymeric peroxides with more than one peroxide moiety per molecule. One suitable initiator has been found to be 'Perhexa MC' (1,1'-di-*tert*butyl-peroxy-2-methyl cyclohexane, Nihon Yusi C.C.). This compound contains two tertiary butyl peroxy groups which allow stepwise polymerisation of the hard and soft segments of the block copolymer. The initiator 'CH-50-AL' (Peroxid-Chemie GmbH) has also been found to be suitable in the manufacture of copolymers suitable for the present invention. An appropriate choice of reaction conditions is well within the skill of one in the art, once a suitable initiator has been chosen.

The initiator is preferably used in an amount of 0.005 - 0.1% by weight of the block copolymer, with 0.01 - 0.05% by weight being particularly preferred, although it will be appreciated that the amount chosen is, again, well within the skill of one in the art. In particular, it is preferred that the amount should not be so much as to cause instant gelling of the mix, nor so low as to slow down polymerisation and to leave excess residual monomers. A preferred level of residual monomers is below 2000 ppm. It will also be appreciated that the amount of initiator will vary substantially, depending on such considerations as the initiator itself and the nature of the monomers.

The block copolymers are adhesives, and preferably are pressure sensitive adhesives. Pressure sensitive adhesives can be applied to a surface by hand pressure and require no activation by heat, water or solvent. As such, they are particularly suitable for use in accordance with the present invention.

The block copolymers may be used without tackifiers and, as such, are particularly advantageous. However, it will be appreciated that the block copolymers may also be used in combination with a tackifier, to provide improved tack, should one be required or desired. Suitable tackifiers are well known and will be readily apparent to those skilled in the art.

Without being constrained by theory, it is thought that the combination of chemical cross-links between the soft segments of the copolymer combined with the, generally, hydrophobic interaction, or physical cross-linking, between the hard portions results in a 'matrix-like' structure. Copolymers having only physical cross-linking of the hard segments are less able to form such a matrix. It is believed that the combination of both forms of cross-linking of the block copolymers provides good internal strength (cohesion) and also high drug storage capacity.

More particularly, it is believed that the hard segments associate to form 'islands', or nodes, with the soft segments radiating from and between these nodes. There is a defined physical structure in the 'sea' between the islands, where the soft segments are cross-linked, so that there is no necessity for extensive intermingling of the soft segments. This results in a greater cohesion of the whole block copolymer while, at the same time, allowing shortened soft segment length and still having as great, or greater, distances between the islands, thereby permitting good drug storage capacity.

The block copolymer preferably cross-links as the solvent is removed, so that cross-linking can be timed to occur after coating, this being the preferred method. Accordingly, not only can the block copolymer easily be coated onto a surface, but the complete solution can also be stored for a period before coating. Accordingly, in the manufacturing process of the patches, the process preferably comprises polymerising the monomeric constituents of each soft segment in solution, then adding the constituents of the hard segment to each resulting solution and polymerising the resulting mix, followed by cross-linking by removal of any solvent or solvent system, such as by evaporation. If the solution is to be stored for any length of time, it may be necessary to keep the polymer from precipitating out, and this may be achieved by known means, such as by suspending agents or shaking. It may also be necessary to select the type of polymers that will be subject to substantially no cross-linking until the solvent is evaporated.

In general, it is preferred that the adhesive possesses a minimum number of functionalities having active hydrogen, in order to avoid undesirable reactions/interactions, such as with any drug that it is desired to incorporate into the adhesive material. It will be appreciated that this is only a preferred restriction, and that any adhesive may be tailored by one skilled in the art to suit individual requirements.

Suitable monomers for use in forming the hard segment include styrene, α -methylstyrene, methyl methacrylate and vinyl pyrrolidone, with the preferred proportion of the hard segment being between 5 and 15 percent w/w. In particular, it is advantageous to use the compounds of WO 99/02141, as it is possible to load over 30 percent of drug into such a system. However, we have found that 20 percent is an acceptable quantity, as compared with the possibility of only 10% or less in conventional patches. Further, it is possible to vary the retained drug according to the requirements of the patient, although these requirements are not as variable as previously, as there is no pre-systemic metabolism.

Thus, in the patches of the present invention, it is generally possible to calculate the amount of drug required and determine the appropriate patch size with a given drug loading in accordance with a patient's body weight, and this can be readily calculated by those skilled in the art.

We have, surprisingly, discovered that the free base of methylphenidate, which is in the form of an oil, is readily incorporated into the preferred adhesives of the present invention. Accordingly, it is readily possible to incorporate the pure methylphenidate into the matrix of the patch, without having to use solubilising agents, for example. In fact, it has been found that, in the matrix form of the patch, it is sufficient for the matrix merely to comprise the adhesive, especially those described above, and methylphenidate.

More particularly, it is preferred to incorporate small amounts of plasticiser, such as isopropyl myristate (IPM). This has the advantage of helping to solubilise the

methylphenidate as well as rendering the adhesive less rough on the skin. Levels of between 2 and 25%, by weight, are generally useful, with levels of between 3 and 20% being more preferred and levels of 5 to 15%, especially about 10%, being most preferred. Other plasticisers may also be used, and suitable plasticisers will be readily apparent to those skilled in the art. In particular, in this embodiment, it is preferred to employ the adhesives of WO 99/02141. It has been found that levels of about 30% methylphenidate are stable in the patches of the invention, with preferred levels being between 15 and 25%, preferably 20%.

Plasticisers generally take the form of oily substances introduced into the adhesive polymer. The effect of the introduction of such oily substances is to soften the physical structure of the adhesive whilst, at the same time, acting at the interface between the adhesive and the skin, thereby helping to somewhat weaken the adhesive, and to reduce exfoliation.

The free base oil may be obtained by basifying methylphenidate hydrochloride, or any other suitable salt, with a suitable base, in the presence of a hydrophilic solvent, especially water, and an organic solvent. We have found that water and ethyl acetate, in approximately equal proportions, work well, with ammonia serving as the basifying agent. The water may then be removed and the preparation washed with further water, or other aqueous preparation, after which the preparation may be suitably extracted with ether, for example, after having removed the ethyl acetate. It is preferred to keep the preparation under an inert atmosphere, especially after completion.

Whilst it will be appreciated that patches of the present invention may be removed from the patient at any time, once it is desired to terminate a given dose, this can have the disadvantage of providing an opportunity for potential drug abuse of the partially discharged patch. Abuse of methylphenidate is highly undesirable.

Instead, what we have found is that it is possible to load a patch of the present invention, especially where it incorporates an adhesive in accordance with

WO 99/02141, such that the patch discharges the majority of the dischargeable load over the desired period, such as 12 hours. After an initial period of about 1-2 hours, the plasma concentrations of methylphenidate, while continuing to show first order absorption kinetics, reach clinically useful levels in a substantially consistent manner, in contrast to oral administration. After the desired period, the plasma concentrations drop rapidly. Thus, patches are exhausted, and not suitable for abuse.

The abuse problems associated methylphenidate tablets may largely be due to the "high" resulting from the rapid increase of methylphenidate in the plasma. With the patches of the present invention, however, levels of methylphenidate increase gradually, so that instant gratification is not possible.

A preferred administration regime is to remove the patch about 4 hours prior to the time at which it is desired to have substantially reduced levels of methylphenidate (usually around 8 hours after application), to provide a particularly advantageous plasma level profile.

Thus, it is a particular advantage, especially of patches using the preferred adhesives, that a patch of the invention can be tailored to have delivered the majority of the methylphenidate that it is capable of delivering, in a 24 hour period, by about 8 hours after application, so that a patch can be left in place, and levels of drug still diminish appreciably. It is advantageous that the drug delivery profile has first order kinetics, so that the majority of the drug is delivered during the main part of the day and, even if the patient omits to remove the patch, the drug is moving towards exhaustion by the end of the day, and the amount of drug is dropping rapidly.

Using the preferred adhesive, a particularly advantageous, first order kinetics drug delivery profile is observed, and there is the added advantage that this particular adhesive will not re-attach after it has been removed. This is especially useful with methylphenidate, as it is a controlled drug which should only be applied to the designated patient.

It will be appreciated that patches of the invention may be constructed in any suitable manner known in the art for the manufacture of transdermal patches. The patches may simply comprise adhesive, drug and backing, or may be more complex, such as having edging to prevent seepage of drug out of the sides of the patch. Patches may also be multi-layered, for example.

The present invention further provides a method of treatment of a patient in need thereof with a patch as disclosed herein. Such methods of treatment are preferred for use on patients having, or potentially having, ADD, ADHD, narcolepsy and/or obesity.

The following, non-binding Examples further illustrate the present invention.

EXAMPLE 1

Preparation of Adhesive Compounds of the Present Invention

The adhesive compound used in the following Examples was made in a two step synthesis:

Step 1:

115g of 2-ethylhexyl acrylate, 84g of diacetone acrylamide, 115g of butyl acrylate and 0.72g tetraethylene glycol dimethacrylate were mixed, in order to obtain a homogeneous solution. The solution was placed in a flask, and 200 cm³ of ethyl acetate along with 200 cm³ of toluene were added. The solution was heated to 80°C under nitrogen, then 0.05 g of 1,1'-di-*tert*-butylperoxy-2-methyl cyclohexane dissolved in 10 cm³ of ethyl acetate were added. Polymerisation was allowed to proceed for 24 hours. This step produced the soft segments.

Step 2:

After 24 hours, 45g methyl methacrylate and 300 cm³ of toluene were added to the mix of Step 1. The solution was then heated to 99°C in order to initiate the second stage polymerisation step, which was continued for 12 hours.

After this time, the polymer was transferred to a bottle for cooling. The resulting solution represented a pre-crosslinked polymer, used in subsequent experiments. The average molecular weight of the polymer produced in this way was estimated to be 358,000 Da by gel permeation chromatography.

At the time of use, methylphenidate and any plasticiser, such as methylphenidate, were blended with the solution, and the resulting mix was cast onto a suitable film, such as a PET film, and dried with heating, suitably at 80°C for 20 minutes.

EXAMPLE 2**Comparison of Base and Hydrochloride Forms of Methylphenidate**

Using the adhesive of Example 1, patches were prepared containing 10% methylphenidate hydrochloride and 5% IPM, or 10% methylphenidate and 5% IPM. The results of *in vitro* human skin permeation tests were as shown in Tables 1 and 2 below.

The skin used was derived from full thickness female skin. The fat and dermis were removed, leaving the stratum corneum and viable epidermis which were mounted on filter paper supports and used to separate the two halves of diffusion cells. The prepared transdermal patches had areas of 0.64 cm², and were pressed firmly onto the skin. The chambers were filled with phosphate buffered saline and maintained at 37°C, thus ensuring the skin surface was maintained at about 32°C. The chambers were

subject to continuous stirring with magnetic fleas. HPLC was used to analyse 200 μ l samples at 215 nm at timed intervals.

Table 1

10% Methylphenidate hydrochloride patch (μ g/cm² penetrated)

	1 hr	2 hrs	4 hrs	6 hrs	8 hrs	12 hrs
Mean	0.00	0.24	2.19	5.27	8.98	19.0

Table 2

10% Methylphenidate free base patch (μ g/cm² penetrated)

Time	1 hr	2 hrs	4 hrs	6 hrs	8 hrs	12 hrs
Mean	0.00	0.51	13.4	44.6	80.0	163

From the above, it can clearly be seen that the base form is clearly superior to the salt in transdermal patches.

EXAMPLE 3

Depletion of Methylphenidate Patches

The accompanying Figures 1 and 2 illustrate the depletion of patches containing 20% methylphenidate and 5% IPM.

More specifically, Figure 1 [Permeation of methylphenidate (μ g/cm²±SE) across human skin in vitro from a patch containing 20% methylphenidate free base in 5% IPM] shows the permeation profile of methylphenidate from a 20% methylphenidate/5% IPM patch. The steady-state flux from this data is 37 ± 4 μ g/cm²/hr. On this basis, a patch of approximately 16 cm² in area would be needed to maintain a therapeutic plasma level of 2 ng/ml in a 30 kg child. Such a high flux from such a low drug loading (0.8 mg/cm²) is

significantly better than prior art patches having a minimum loading of 2.7 mg/cm² in order to produce therapeutic plasma levels of methylphenidate.

A result of this high flux from low drug loading is the high level of drug depletion from the patch achieved. Figure 2 [Permeation of methylphenidate (%) across human skin *in vitro* from a patch containing 20% methylphenidate free base in 5% IPM] shows the data in Figure 1 normalised for the applied dose of methylphenidate. What is demonstrated is that, after 12 hours, the level of drug in the patch was depleted by almost 50%. This level of depletion is advantageous in reducing possible abuse and for considerations of toxicology and economy.

Furthermore, the drug release kinetics can be manipulated so that the "tail-off" in delivery (first order kinetics) becomes more pronounced (Figure 3, *infra*). This may prove advantageous over so-called zero-order release devices because the dose required by a patient towards the end of a day is lower than during the day (methylphenidate is a stimulant also used to treat narcolepsy, hence excessive doses of drug towards the end of a day may cause unwanted wakefulness in patients).

EXAMPLE 4

Depletion of Patches with Differing Amounts of IPM

The accompanying Figure 3 [permeation ($\mu\text{g}/\text{cm}^2 \pm \text{SE}$) of methylphenidate from patches containing 5, 10 and 20 % IPM] illustrates the effect of IPM on permeation of methylphenidate. It can be seen that increasing the level of IPM above 5% shows no advantage in permeation studies, so that there is no economic reason to use higher levels. It can also clearly be seen that the first order nature of release of drug is reflected *in vivo*, where blood levels of the *d* and *l* enantiomers drop after about 10 hours even if the patch is left in place for 24 hours. The difference between this situation and that in which the patch was removed at 8 hours is surprisingly small.

EXAMPLE 5

Profiles of Plasma Levels

Plasma levels for 10% concentrations of the *d* and *l* enantiomers of methylphenidate in patches were measured and are shown in Figure 4.

It can clearly be seen that substantial quantities of the *l* enantiomer are entering the bloodstream.

In Figure 5, the effect of delivering methylphenidate from a patch of the invention is shown compared to administration of Ritalin tablets. The advantages are clearly shown in the consistent plasma levels obtained.

EXAMPLE 6

Preparation of the Free base Form of Methylphenidate

A 20 litre vessel was charged with 5.7 litres of water. Subsequently, methylphenidate hydrochloride was added in a quantity of 1.3 kilograms and, finally, 5.75 litres of ethyl acetate was added to the vessel. The resulting mixture was stirred at a temperature of between 15 and 20°C.

After mixing of the ingredients, ammonia (d 0.88) was added to the mixture until the pH rose to between 9.5 and 10. Approximately 0.3 litres of ammonia solution is generally sufficient. After addition of the ammonia, the contents are stirred for a further 5-10 minutes at between 15 and 25°C.

After this time, the contents were allowed to settle, and the lower aqueous phase was removed and discarded. 3 litres of water were then added to the mixture and the contents stirred for 5-10 minutes. Once again, the contents were allowed to settle and the aqueous removed and discarded. This washing step was repeated one further time.

After discarding the final aqueous phase, the container was set for vacuum distillation in order to remove the ethyl acetate. The internal temperature of the flask was raised to 50°C under a vacuum of at least -0.9 Bar. A rotary evaporator may be used at this stage.

10 litres of absolute alcohol (100 percent ethanol) was added to the oil left after the vacuum distillation, and the resulting ethanol solution was polish filtered (1µm) into a rotary evaporator flask. The ethanol was then distilled off under vacuum, the water bath of the rotary evaporator being allowed to reach 50°C. In order to evaporate off as much ethanol as possible, it is preferred to raise the vacuum to at least -0.95 Bar towards the end of the evaporation process.

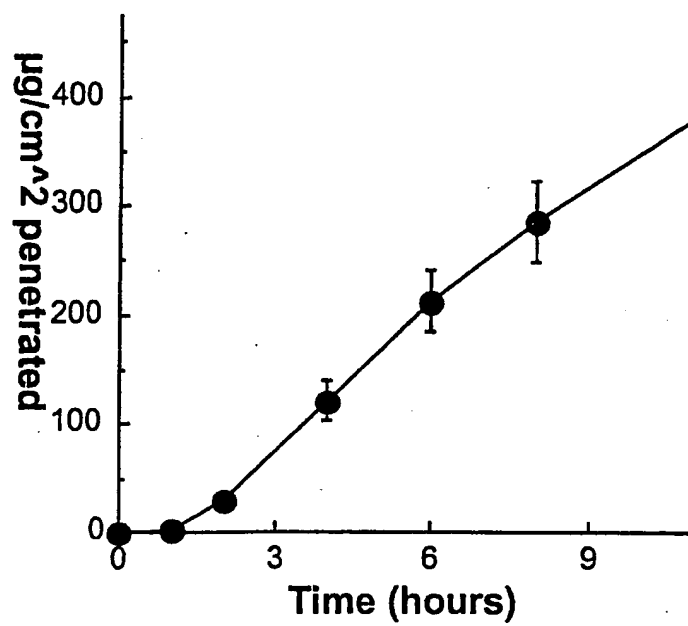
Once the ethanol had been removed, the resulting oil was stored under a nitrogen atmosphere.

Yield, 1.1 kilogram.

CLAIMS:

1. A transdermal patch comprising the free base form of methylphenidate, wherein the patch is capable of delivering 40% or more of the total methylphenidate therein within 12 hours, *in situ*.
2. A transdermal patch comprising the free base form of methylphenidate, wherein the methylphenidate is retained by the adhesive, the adhesive comprising a cross-linked block copolymer having drug retention properties, the block copolymer having hard and soft segments, and wherein there is cross-linking between the soft segments.
3. A patch according to claim 2, capable of delivering 40% or more of the total methylphenidate therein within 12 hours, *in situ*.
4. A patch according to any preceding claim, containing less than 1.2 mg methylphenidate per cm² thereof and suitable to sustain a plasma level of between 2 ng/ml and 5 ng/ml in a 30 kg human after attachment to the skin thereof for at least 3 hours for a period of at least 3 hours.
5. A patch according to any preceding claim, containing between 0.6 and 1.2 mg methylphenidate per cm².
6. A patch according to any preceding claim, wherein the adhesive comprises a plasticiser.
7. A patch according to claim 6, comprising between 3 and 20% by weight of plasticiser.
8. A patch according to claim 7, comprising between 5 and 10% of plasticiser.

9. A patch according to any of claims 6 to 8, wherein the plasticiser is isopropyl myristate.
10. A patch according to any preceding claim, wherein the adhesive is chemically neutral.
11. A patch according to any preceding claim, wherein methylphenidate is present in an amount of between 10 and 30% by weight of the adhesive.
12. A method of treatment of a condition susceptible to treatment with methylphenidate in a patient in need thereof comprising applying a patch according to any preceding claim to the skin of said patient.
13. A method according to claim 12, wherein the condition is selected from the group consisting of Attention Deficit Disorder, Attention Deficit Hyperactive Disorder, narcolepsy and obesity.

**FIG. 1**

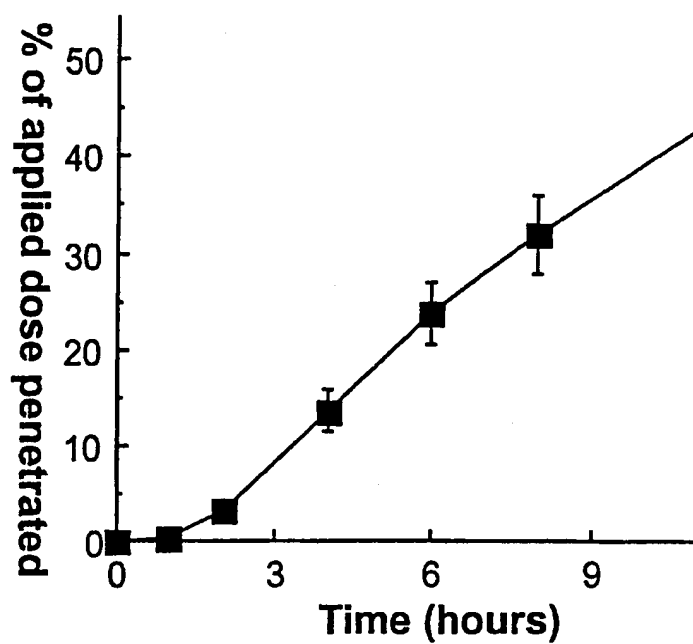


FIG. 2

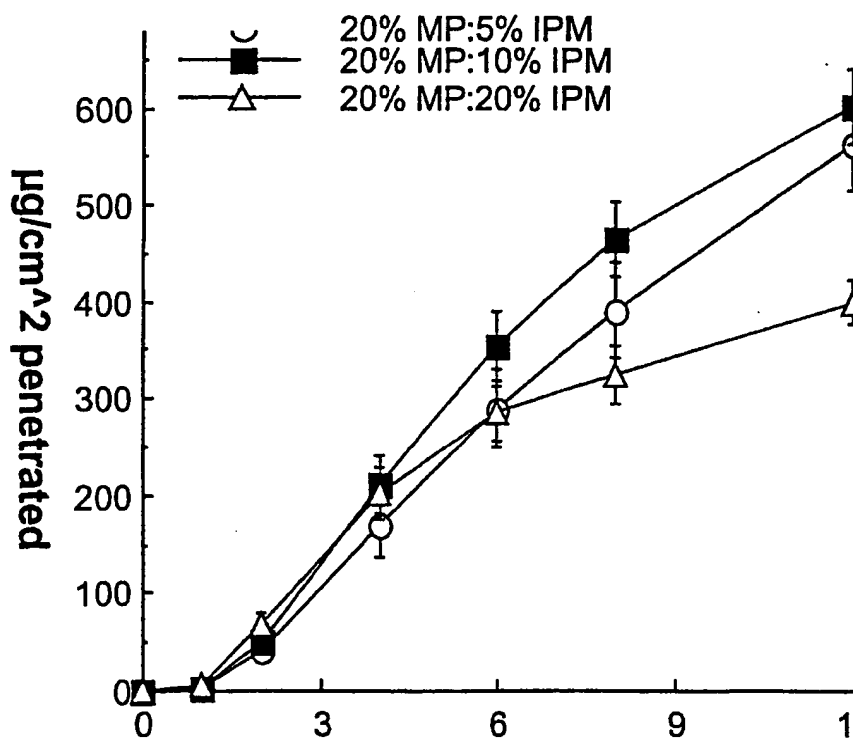
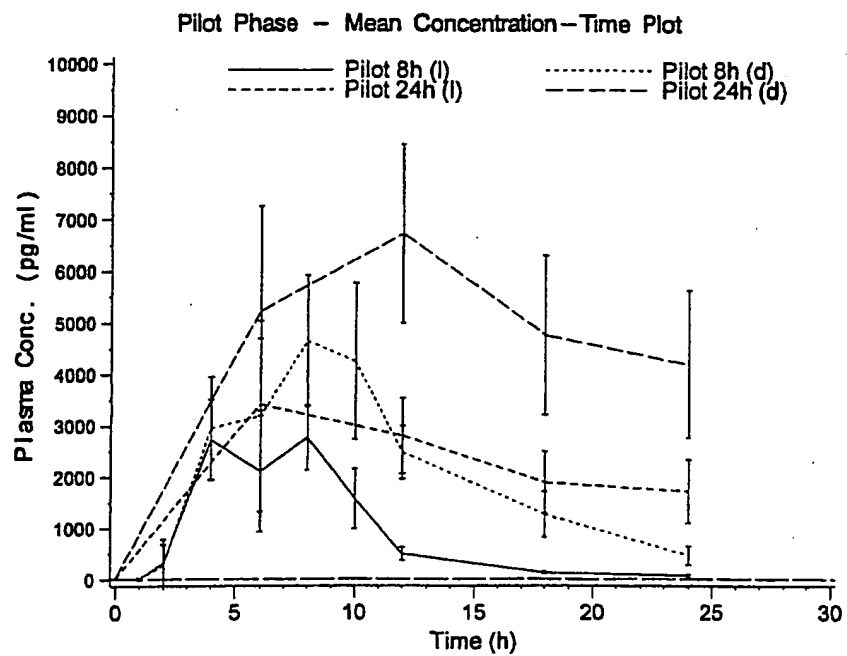
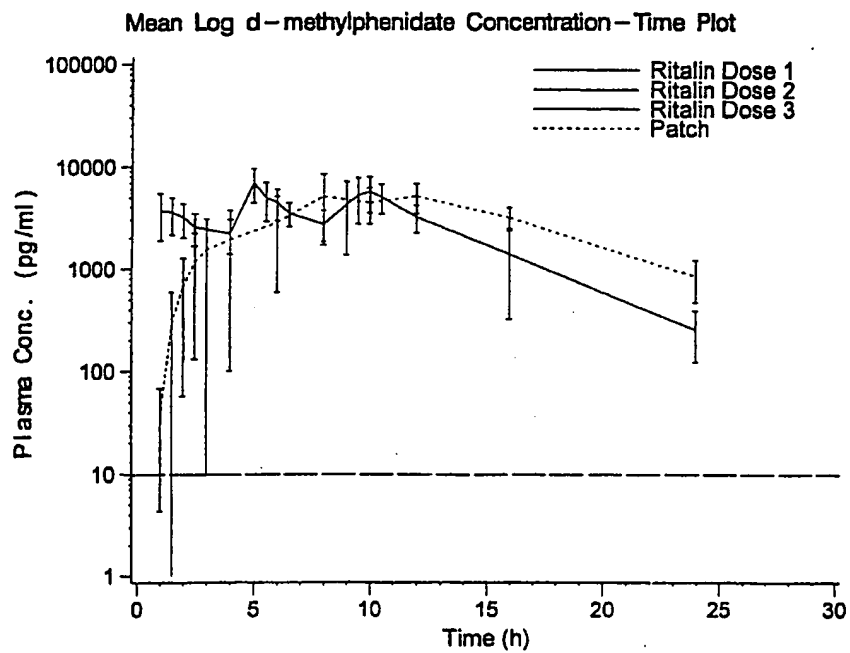


FIG. 3

3/3

**FIG. 4****FIG. 5**

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/03060

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/70 A61K31/445 A61P3/04 C08F265/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C08F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 30694 A (MANTELLE JUAN ;DIXON TERESE A (US); NOVEN PHARMA (US)) 24 June 1999 (1999-06-24) cited in the application	1,6, 10-13
A	page 4, paragraph 2 -page 5, paragraph 4 page 7, line 7 - line 9 page 7, paragraph 3 -page 8, line 7 page 8, line 17 - line 21 page 8, last paragraph -page 9, paragraph 1 page 9, paragraph 3 page 10, paragraph 3 page 10, line 6 page 12, line 12 - line 29 page 13, paragraph 4 -page 14, paragraph 1; claims 1,2,5-7,10,14-21; examples --- -/--	2-5,7,8



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

8 December 2000

Date of mailing of the international search report

27/12/2000

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INTERNATIONAL SEARCH REPORT

Internat. Application No

PCT/GB 00/03060

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 834 010 A (VENKATESHWARAN SRINIVASAN ET AL) 10 November 1998 (1998-11-10) cited in the application column 1, line 9 - line 15 column 2, line 21 - line 23 column 2, line 41 - line 48 column 3, line 48 - column 4, line 14 column 5, line 31 - line 44 column 5, line 62 - line 66 column 7, line 1 - line 3; claims 1-3,6,13,14; example 5	1,4,6,7, 10
X	EP 0 881 216 A (JOHNSON MATTHEY PLC) 2 December 1998 (1998-12-02) cited in the application page 2, column 1, line 3 - line 12 page 2, column 1, line 22 - line 31 page 3, column 3, line 15 - line 36 page 3, column 3, line 46 - line 53; claims 1-3,5-7	1,12,13
A	WO 99 02141 A (STRAKAN LIMITED ;KAMIYAMA FUMIO (JP)) 21 January 1999 (1999-01-21) cited in the application page 1, paragraph 1 - paragraph 2 page 2, paragraph 3 page 3, paragraph 4 - last paragraph page 11, paragraph 2 - paragraph 4; claims; examples 1,2	2-11
T	WO 00 44846 A (STRAKAN LIMITED ;KAMIYAMA FUMIO (JP)) 3 August 2000 (2000-08-03) cited in the application page 1, paragraph 5 page 2, last paragraph -page 3, paragraph 1 page 5, paragraph 3 page 11, paragraph 2; claims 1,6,15; example 1	2-11
A	REYNOLDS JEF: "Martindale. The Extra Pharmacopoeia. 31st Edition." 1996 , ROYAL PHARMACEUTICAL SOCIETY , LONDON XP002154970 page 1553, column 3, paragraph 5 -page 1554, column 1, paragraph 1	12,13

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

Present claim 1 relates to a product defined by reference to a desirable characteristic or property, namely a patch capable of delivering 40% or more of the total methylphenidate therein within 12 hours, in situ. The claim covers all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the product prepared in examples 1-5 and the concept of a patch that is capable of delivering 40% or more of the total methylphenidate therein within 12 hours in situ.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/03060

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WO 0044846 A	03-08-2000	AU 2121600 A	18-08-2000